CURRENT TOPIC

Status epilepticus: pathophysiology, epidemiology, and outcomes

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Convulsive status epilepticus (CSE) is the most common neurological medical emergency and continues to be associated with significant morbidity and mortality. Our approach to the epilepsies in childhood has been clarified by the broad separation into benign and malignant syndromes. The factors that suggest a poorer outcome in terms of seizures, cognition, and behaviour include the presence of multiple seizure types, an additional, particularly cognitive disability, the presence of identifiable cerebral pathology, a high rate of seizures, an early age of onset, poor response to antiepileptic drugs, and the occurrence of CSE.[1]

Convulsive status epilepticus is not a syndrome in the same sense as febrile convulsions, benign rolandic epilepsy, and infantile polymorphic epilepsy. These latter disorders have a tight age frame, seizure semiology, and a reasonably predictable outcome. Episodes of CSE can occur in each: occasionally in febrile convulsions, rarely in benign rolandic epilepsy, and often in infantile polymorphic epilepsy. The issue of whether episodes of status epilepticus are intrinsically more dangerous in the malignant syndromes needs consideration before we accept global figures for CSE outcome, and we need to separate the immediate outcome of CSE from the eventual outcome, which may be heavily influenced by the context or syndrome in which it occurs.

In practical management we are likely to want to stop prolonged seizures as soon as possible, but in theoretical terms it may be important to know if some causes of CSE are intrinsically more dangerous. The paediatric dimension to CSE is therefore of many different causes and occurring in a patient who is less likely to have concomitant cardiovascular or respiratory disease. The hazards and outcome might be different. This paper reviews advances in the pathophysiology and consequences of CSE with special reference to age related phenomena.

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Definition

Status epilepticus is a disorder in which the mechanisms required for seizure termination fail. This definition, unfortunately, is not clinically useful as these mechanisms have not yet been well described. The most widely used definition is a seizure or series of seizures that last for 30 minutes or more, without full consciousness being regained between the seizures. This gives the impression that status epilepticus is always convulsive and is a single entity. There are, however, as many types of status epilepticus as there are types of seizures, and this definition is now probably outdated.

To show that status epilepticus is a complex disorder, Shorvon has proposed the following definition. Status epilepticus is a disorder in which epileptic activity persists for 30 minutes or more, causing a wide spectrum of clinical symptoms, and with a highly variable pathophysiological, anatomical, and aetiological basis.[2] CSE needs different definitions for different purposes. Many seizures that last for five minutes will continue for at least 20 minutes, and so treatment is required for most five minute seizures. Therefore for emergency treatment purposes the definition should state a time of five minutes, and means that the child is at risk of having a seizure lasting 20 minutes or more. However, for pathophysiological, epidemiological, and outcome purposes a definition of seizures persisting for at least 20 minutes seems appropriate to identify those at risk of developing structural brain damage. There is currently no consensus on a definition.

Pathophysiology

Much of the work described in this section has been carried out in human adults and animal models, and we must be cautious about extrapolating this information into childhood.

SEIZURE INITIATION AND PROLONGATION

Why seizures start and stop is unknown, although it is likely that seizure initiation is caused by an imbalance between excitatory and inhibitory neurotransmission, leading to the initiation of abnormal neural impulses. The seizure threshold in the immature brain appears to be lower than in the mature brain, but the mechanisms that underlie this susceptibility remain unclear. Excitatory synapses mature earlier than inhibitory synapses and this, coupled with an increase in the susceptibility of excitatory neurotransmitter receptors, increases the likelihood that an excitation–inhibition imbalance may occur.[3 4]

There are other important differences between the immature and adult brain. Stimulation of $GABA_A$ receptors in the immature brain

Table 1 Systemic and cerebral pathophysiological changes associated with seizures and convulsive status epilepticus

Compensation (< 30 minutes)	*Decompensation (> 30 minutes)*
Increased cerebral blood flow	Failure of cerebral autoregulation
Cerebral energy requirements matched by supply of oxygen and glucose	Hypoglycaemia
Increased glucose concentration in the brain	Hypoxia
Increased catecholamine release	Acidosis
Increased cardiac output	Hyponatraemia
	Hypo/hyperkalaemia
	Disseminated intravascular coagulation
	Leucocytosis
	Falling blood pressure
	Falling cardiac output
	Rhabdomyolysis

results in depolarisation rather than hyperpolarisation, as occurs in the adult brain.[5] The immature cerebral cortex has a high synaptic density at around 2 months of age and this may contribute to the development of hypersynchrony of neural groups.[4]

The excitatory amino acid neurotransmitter glutamate increases at the site of the seizure focus at the beginning of seizure activity in adults with temporal lobe epilepsy when measured by in vivo intracerebral microdialysis.[6 7 8] It is believed that the same may happen at the onset of generalised seizures. Inhibitory neurotransmitters such as GABA later increase at the seizure focus and redress the balance between excitation and inhibition.[6] GABA also increases in the substantia nigra pars reticulata, an area that can modulate a cortical inhibitory response in adult rats, but not in immature rats.[3] Other mechanisms of inhibitory receptor modulation, such as adenosine receptor agonism, may also contribute to seizure termination. Thus the increased incidence of CSE in childhood is probably caused by a combination of increased seizure susceptibility and decreased ability to mount an adequate inhibitory response.

SYSTEMIC AND CENTRAL PATHOPHYSIOLOGY

The systemic effects of CSE are initially dominated by the body's attempt to maintain homeostasis.[9] Blood pressure and central venous pressure increase, blood glucose increases, and the patient becomes tachycardic.[9 10] CSE may also result in electrolyte imbalance and hyperthermia.[11] Cerebral blood flow, blood glucose, and oxygen utilisation increase in the initial phases of a seizure to maintain cerebral homeostasis. After 30 minutes homeostatic failure begins and the patient may need systemic support.[9] Cerebral blood flow, brain glucose, and parenchymal oxygenation all decrease and potentially play a part in the cell damage associated with CSE.[9 10] Respiratory and metabolic acidosis, electrolyte imbalance (for example, hyperkalaemia), hyperthermia, and rhabdomyolysis may all occur (table 1).Treatment with drugs with depressant cardiorespiratory side effects (for example, benzodiazepines and barbiturates) may worsen the systemic complications of CSE.

ELECTROPHYSIOLOGY

About 70-80% of cases of CSE throughout all age groups will have a focal onset but be secondarily generalised. A predictable sequence of changes in the electroencephalogram (EEG) has been shown in adult humans and in at least six animal models.[12] CSE starts with localised epileptic activity followed by isolated generalised bursts of seizure activity with a normal EEG in between. If the patient does not regain consciousness between these episodes, then they meet the clinical criteria for CSE. The isolated ictal discharges merge and become a continuous discharge after about 30 minutes. Discharges then fragment and are interspersed with flat periods. Ultimately, periodic epileptiform discharges, which may reflect underlying metabolic failure, will occur.[9 12]

The motor phenomena associated with CSE follow a similar pattern to the EEG changes. Recurrent seizures will merge into continuous motor activity, followed by fragmentation of the motor activity and myoclonus. If the seizure persists, then electromechanical dissociation will ensue.[9 12] The prognosis for a good neurological outcome decreases the further the patient moves through this continuum.

ROLE OF EXCITOTOXIC AMINO ACIDS IN THE DEVELOPMENT OF STRUCTURAL BRAIN DAMAGE SECONDARY TO CSE

Mesial temporal sclerosis is the most common acquired brain lesion following CSE and may result from excitotoxicity. Most work in this field has been directed at the effects of glutamate. Lucas and Newhouse, 36 years ago, observed that systemic glutamate destroyed retinal cells in rat pups.[13] They suggested that glutamate was directly responsible for the cell death, although the neurotransmitter role of glutamate was unknown. Since that time much animal model and cell culture work has attempted to prove this hypothesis and to relate it to status epilepticus.[14] Direct application of glutamate onto hippocampal cultures causes neuronal death, which resembles that seen in the animal models described in the following section.[15] This work provides indirect evidence that CSE can itself cause hippocampal damage.

Animal model

Convulsive status epilepticus has been induced in animal models with the use of convulsant chemicals or by electrical kindling.

- Anti-GABA drugs—bicucculine given to adolescent baboons[16] results in neuronal loss in the hippocampus, neocortex, amygdala, thalamus, and cerebellum. The hippocampal cell loss resembles that seen in humans who have died during CSE.[17] Allylglycine

can also cause cell death when administered systemically.[9 18]

- Glutamatergic drugs—kainic acid is a glutamate agonist that has been widely used to induce status epilepticus. Hippocampal damage is seen after CSE in rats exposed to intraperitoneal, intra-amgydala, or intraventricular kainic acid. This damage is seen in similar areas of the hippocampus to that seen in humans who have died during CSE.[2] Other drugs that have been used include N-methyl-D-aspartate (NMDA), quisqualate, and pentylenetetrazol.[9 18]
- Cholinergic drugs—pilocarpine and dipiperidionethane cause CSE in rats, and result in damage prominent in the neocortex, thalamus, amygdala, and hippocampus.[9]
- Electrical stimulation models have also been developed and show that neuronal death occurs in the hippocampus if continuous protocols are followed.

Thus many different experimental paradigms result in similar damage to the hippocampus, and the damage is probably caused by the presence of status epilepticus itself and not a direct effect of the drug used to provoke status epilepticus. Bilateral hippocampal damage may occur even with unilateral stimulation.[9 18]

Rats that have been exposed to kainate after they have been rendered epileptic by electrical kindling methods do not appear to develop as much hippocampal damage as non-epileptic rats. The kindled animals had a different seizure semiology in that their seizures tended to be restricted to the limbic system and were longer lasting.[19] CSE induces the production of heat shock proteins in several brain regions.[20] The presence of heat shock proteins can protect the brain against further stressful stimuli, which are potentially damaging to neurones.[21] The implication is that prolonged seizures may need to occur in epilepsy naive human patients for mesial temporal sclerosis to develop, and that once it has developed further episodes of CSE may not worsen the mesial temporal sclerosis.

MECHANISMS BY WHICH GLUTAMATE CAUSES CELL DEATH

Excess extracellular glutamate may result in cell death by causing necrosis, gene determined cell death, or both.[9] The primary receptor involved in cytotoxicity related to glutamate is the NMDA receptor, although other glutamate receptors may be involved.[2 9 13] The NMDA receptor is an ionotropic receptor. Binding of glutamate and glycine or D-serine to appropriate sites on the receptor results in an influx of calcium through the ionophore. High intracellular calcium concentrations result in the activation of a large number of calcium dependent processes such as those described in the following.

- Activation of protein kinase C. This enzyme is moved from the cytosol to the cell wall, resulting in destruction of the wall.[13]
- Nitric oxide and free radical formation. Calcium stimulates constitutive nitric oxide synthase, causing an increase in intracellular nitric oxide.[22] Nitric oxide can inhibit mitochondrial respiration directly or indirectly by forming peroxynitrite free radicals, which are cytotoxic.[13 22]
- Activation of phospholipase A_2. This enzyme breaks down membrane lipids with the release of arachidonic acid and other fatty acids. One consequence of this membrane destruction can be cell death.[13]
- Activation of protease calpain I. The mechanism by which this enzyme causes cell death is unclear, but calpain I inhibitors are partially neuroprotective.[13]

Glutamate receptor stimulation also results in the formation of immediate early genes, such as c-fos, fos-B, c-jun, and jun-B. c-fos encodes for Fos protein, which has a leucine zipper allowing it to bind and form dimers with similar proteins. These dimers bind to a specific DNA region (AP-1 site), which regulates the expression of a number of late effector genes.[23] Some of the genes regulated are harmful and some are potentially neuroprotective. Thus immediate early genes may play a dual role: induction of gene determined cell death and activation of brain repair mechanisms.

Metabotropic glutamate receptors are not directly associated with an ion channel, and stimulation of these receptors results in the formation of intracellular second messengers. These receptors may also have toxic and protective functions. The potentially toxic effects of metabotropic glutamate activation include the potentiation of NMDA and other excitatory membrane currents, the potentiation of intracellular calcium release, a decrease in inhibitory membrane currents, and decreased GABAergic inhibition. Conversely, potential protective effects include the inhibition of synaptic glutamate release and decreased calcium influx.[24] Clearly further work related to the functions of immediate early genes and metabotropic glutamate receptors is required.

Equal hippocampal damage does not occur across all ages in rats. Neonatal rats are relatively resistant to the development of hippocampal damage after CSE. Maximum vulnerability occurs in P18 to P21 rats, with less vulnerability of hippocampal neurones in adult rats. Changes in humans appear to reflect the changes seen in rats. Children who develop CSE in the neonatal period do not appear to develop mesial temporal sclerosis, but others are most vulnerable under the age of 3 years.

Epidemiology, aetiology, and outcome

In terms of outcome it is useful to divide the aetiologies of CSE into febrile and non-febrile. Febrile CSE (status epilepticus associated with fever in a neurologically normal child between the ages of 6 months and 5 years) is considered to have a good prognosis. There is a very low incidence of new neurological deficits or cognitive impairment in this group of children, but the risk of subsequent epilepsy appears to be 21%,[25] much higher than the population risk of epilepsy (0.5–1%). About half of these children will go on to have complex partial seizures,[25] many of whom will have mesial temporal sclerosis. The relation between CSE and

mesial temporal sclerosis is presumed to be causative, although this is not proved. Up to 75% of children with temporal lobe epilepsy will have evidence of mesial temporal sclerosis on magnetic resonance imaging,[26 27] suggesting that mesial temporal sclerosis in childhood is not as rare as previously believed and is probably underdiagnosed. Approximately 50% of patients with temporal lobe epilepsy secondary to mesial temporal sclerosis will have a history of prolonged febrile convulsions in childhood.[2]

Outcome from non-febrile CSE is primarily dependent on the aetiology, which is in turn dependent on the age of the child.[28–31] CSE lasting longer than one hour has a higher mortality than CSE lasting less than one hour.[31] The aetiology of non-febrile CSE can be divided into three groups. (a) idiopathic; (b) acute symptomatic—for example, meningitis, encephalitis, stroke, acute metabolic disorders; and (c) remote symptomatic—for example, underlying acquired, developmental or congenital CNS disorder; this category also includes CSE occurring in children with defined epileptic syndromes.

Cognitive or persistent neurological deficits and further seizures occur most frequently with symptomatic aetiologies and in children under the age of 3 years. It is possible that the prognosis of an underlying disorder is worsened by an episode of CSE, but it may be difficult to tease out the significance of the episode of CSE.[29] Recurrent CSE occurs in about 17% of children after an initial episode of CSE. Forty four per cent of these children will have underlying chronic brain disorders and 11% will have initially presented with an acute cerebral insult.

Two metabolic disorders that may present with CSE deserve special mention as they are treatable. Pyridoxine dependent epilepsy may present in the neonatal period, but it usually presents with seizures when the child is a few months old. Treatment with pyridoxine controls the seizures. All children under the age of 18 months with intractable seizures should have a trial of pyridoxine. Biotinidase deficiency is one biochemical defect in biotin responsive multiple decarboxylase deficiency. Children classically develop seizures, ataxia, skin rash, and alopecia, but may present with seizures alone. Biotin given by mouth is an effective treatment.

There has been an apparent decrease in mortality since Aicardi and Chevrie[32] published their review of 239 episodes of CSE in 1970. They showed a mortality of 11% and a poor neurological or cognitive outcome in 53% of patients. The hemiconvulsion, hemiplegia epilepsy syndrome seen in this series is now a rare complication of CSE and occurs only in children in whom a seizure has lasted more than one hour. By 1989 the mortality had decreased to between 3% and 6%.[28 30 33 34] The incidence of prolonged seizures was possibly higher when the Aicardi and Chevrie series was being collected as benzodiazepines had not been introduced into clinical practice. A change in definition may also have played a part. Aicardi and Chevrie required that seizures lasted at least one hour, whereas the more recent studies use 30 minutes as the cut off point. The longer a seizure lasts, the more difficult it becomes to treat, increasing the likelihood of a poor outcome.[2] In a retrospective 10 year review of intensive therapy unit admissions for CSE the mortality was 8%, although 12% of children had died within one year. Thirty three per cent had neurological sequelae ranging from minor motor problems to persistent vegetative states.[35] All of these studies have a bias in their methodology as all the patients were recruited from hospital based populations.

There are few prospective epidemiological studies attempting to define clearly the incidence and outcome of CSE. This is because they are difficult to perform, requiring a network between all hospitals in a delineated area and many person-hours to ensure data collection before patient discharge. It is clear that retrospective work is less accurate, as note keeping in hospitals is usually not accurate enough to obtain sufficiently good data. DeLorenzo *et al* in Richmond, Virginia performed such a study in which only people living within the city limits were included.[36] The hospital network went beyond the city limits and therefore patients presenting outside their area were identified. The success of this study depended on a status epilepticus research team being on call 24 hours a day, seven days a week. Patients were reported to the team on admission, but the team also identified patients by using the ICD 9 codes for seizures. The notes of all patients were reviewed by the team. The total incidence of CSE was 41/100 000 residents, but this figure was 147/100 000 in infants aged 1 month to 1 year. Further episodes of CSE were identified in 35% of these children. Partial and secondary generalised seizures accounted for most of the episodes of CSE in the paediatric age group, although primary generalised CSE occurred in 45% of cases. Despite having the highest incidence of CSE, the mortality in children was only 2.5%, and non-central nervous system infections accounted for all the deaths in this study.[36]

The child health and education survey is a population based birth cohort study in which 14 676 children born in a single week in 1970 have been followed for 10 years. Thirty seven of these children had at least one episode of CSE by the time they were 10 years old. Nineteen had lengthy febrile convulsions and 18 had non-febrile status epilepticus. Two children died (5.4%), both of whom presented with non-febrile CSE. New neurological signs were identified in only one child.[25] Twenty one per cent of children developed non-febrile seizures after a prolonged febrile convulsion. The national collaborative perinatal project was an epidemiological study carried out in the USA, which showed that 5.4% of children developed non-febrile seizures after a prolonged febrile seizure by 7 years of age.[37] Despite the fact that outcome seems to be improving, the possibility of a poor prognosis after CSE is still great

enough to be of concern. There is a lag period from the time of a prolonged febrile seizure to the development of complex partial seizures, and therefore these studies probably underestimate the risk of subsequent epilepsy and longer follow up periods are required.

Finally, these studies do not address the question of whether mesial temporal damage which is not epileptogenic, may cause cognitive, especially memory, impairment. Such damage is apparent in the contralateral temporal lobe of many children and adults investigated for surgical treatment of mesial temporal sclerosis.[27] There is evidence that such damage may be of cognitive significance.[38]

Conclusions

Convulsive status epilepticus continues to be associated with significant neurological morbidity and mortality. It is therefore important that the disorder is recognised rapidly and treatment instituted as soon as possible. Although the outcome is dependent on aetiology, it is believed that appropriate early management may reduce some of the morbidity associated with CSE. Future therapeutic and neuroprotective interventions need to be investigated in the light of our current understanding of the mechanisms of seizure termination and neuronal death. The incidence of CSE is highest in childhood and therefore neuroprotective strategies may ultimately be most usefully carried out in children.

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